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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PDL BIOPHARMA, INC. and EKR THERAPEUTICS, INC., Plaintiffs, v. SUN PHARMACEUTICAL INDUSTRIES LTD., Defendant.	Civil Action No. 07-1788 (KSH)(PS) Hon. Katharine S. Hayden, U.S.D.J. Hon. Patty Shwartz, U.S.M.J. **CONFIDENTIAL MATERIAL REDACTED PURSUANT TO L. CIV. R. 5.3(C)(3) MOTION TO SEAL PENDING** **(Filed Electronically)** **Oral Argument Requested**

PDL AND EKR'S REPLY IN SUPPORT OF THEIR CROSS-MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT

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I. INTRODUCTION

What is most striking about Sun's Reply and Opposition is what Sun does not say, rather than what it does. Sun studiously avoids mentioning the instruction in its package insert [redacted] Just as it adds [redacted] or any other ingredient, Sun adds the instruction to ensure that its composition is [redacted] Sun never squarely responds to Plaintiffs' particularized evidence that the [redacted]

By not addressing the specifics of Plaintiffs' infringement analysis, Sun leaves key facts completely unrebutted. Sun does not dispute that the instruction is a required part of its product, that FDA approval is contingent on the instruction being included as part of Sun's product, or that its composition is rendered isotonic when [redacted]

Sun states that its product is "very different" from the '405 composition without providing a substantive explanation why the [redacted] is a substantial difference from the perspective of either a formulator or clinician. In light of its representations to the FDA, Sun must concede that its product has comparable stability, safety, and efficacy as Cardene®

I.V., the preferred embodiment of the '405 patent. Accordingly, Sun is unable to rebut the overwhelming evidence in Sun's own documents, the testimony of its witnesses, and the opinions of Plaintiffs' experts demonstrating that the sorbitol and instruction in Sun's product perform substantially the same function in substantially the same way to achieve substantially the same result as the claimed non-chloride compound.

Sun backs away from its argument that the difference in [redacted] matters because its composition, [redacted] Sun downplays the safety argument that it trumpeted loudly in its earlier summary judgment briefs, presumably because Sun recognizes that this argument directly contradicts its representations to the FDA that its product should be approved as a safe and effective generic substitute for Cardene® I.V.

Instead, Sun retrenches by arguing that its product does not infringe because the '405 claims are limited to compositions that are directly injected from the ampul. But nothing in the '405 claims, specification, or prosecution history indicates that the inventors gave up compositions that are administered by infusion. Indeed, the exact opposite is true. The inventors describe at length their work to solve stability problems with nicardipine hydrochloride solutions after dilution, particularly in 5% dextrose. That work is every bit a part of their invention as their work to stabilize nicardipine hydrochloride solutions during the manufacturing

process and storage. Sun attempts to read limitations and disclaimers into the '405 patent and prosecution that are simply not there.

Sun has failed to make a showing necessary to overcome Plaintiffs' detailed evidence of infringement. At the very least, therefore, there is a material issue of fact for trial, and Sun's motion for summary judgment should be denied. But given the overwhelming evidence that Sun's product infringes under the doctrine of equivalents and Sun's lack of any meaningful rebuttal, summary judgment of infringement is warranted in this case.

II. SUN'S PRODUCT INFRINGES UNDER THE DOCTRINE OF EQUIVALENTS

Sun's arguments all stem from the single contention that its product does not infringe the limitation "isotonic." Notably absent from Sun's opposition to Plaintiffs' cross-motion are any additional reasons why Sun's product allegedly does not infringe claims 1, 3 and 4. Thus, Sun implicitly concedes that its product literally infringes every other limitation of those claims. And as discussed below, Sun has failed to rebut the overwhelming evidence that Sun's product infringes the isotonic limitation under the doctrine of equivalents.[1]

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[1] Sun disputes that its [redacted] infringes the terminal autoclaving step recited in claim 2. (*See* Sun's Opposition and Reply ("Opp'n") at 6 n.2). That limitation, however, is not at issue for purposes of the parties' cross-motions, and does not preclude summary judgment of infringement with respect to claims 1, 3 and 4.

A. Sun Mischaracterizes Plaintiffs' Infringement Contentions

Sun is wrong when its says Plaintiffs "never assert[] that any single form of Sun's product" infringes. (*See* Opp'n at 1). Plaintiffs' opening brief could not be clearer. The infringing product in this case is the nicardipine hydrochloride product that Sun describes in its ANDA. (Br. at 29-30). The infringement issue is that Sun's product, as packaged and labeled for use, is equivalent to the isotonic composition of the '405 claims. As set forth in Plaintiffs' opening brief, Sun's product is equivalent from a formulator's point of view because it takes advantage of every benefit of the '405 composition, particularly with respect to stability. (Br. at 31-33). Sun's product is also equivalent from a clinician's point of view because, as labeled, there is no difference to the patient with respect to safety or efficacy. (Br. at 33-34). Sun has gone to great lengths to persuade the FDA on all these points – *i.e.*, that its product has comparable stability, safety, and efficacy to the preferred embodiment of the '405 patent, Cardene® I.V. Sun never addresses these issues head on. Accordingly, its arguments completely miss the mark.

Instead, Sun directs its arguments to oversimplified and distorted versions of Plaintiffs' contentions. (*See* Opp'n at 1, 3, 6, 7). It sidesteps the key questions, and in doing so, leaves Plaintiffs' particularized evidence of why Sun's ANDA product infringes under the doctrine of equivalents unrebutted. Perhaps the most glaring example is that Sun offers ***no declaration from any expert*** to address any

point in Plaintiffs' doctrine of equivalents analysis of function, way, and result. Sun relies only on conclusory attorney argument, which does not come anywhere close to rebutting Plaintiffs' evidence in support of summary judgment. *See Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1380-81 (Fed. Cir. 2006).

Finally, Sun argues that Plaintiffs "refused" to admit that "Sun's concentrated form is not isotonic and that Sun's diluted form is not concentrated." (Opp'n at 1, 5-6). Plaintiffs dispute Sun's contentions for good reason – Sun's product plainly has the required amount of nicardipine hydrochloride and is equivalent to the isotonic composition of the '405 claims. Plaintiffs made their position clear in their opening brief and in response to Sun's Rule 56.1 statement based on the documents, testimony, and expert opinions in this case. Rather than "refus[ing] to take any position," as Sun contends, Plaintiffs' well-founded responses highlight the central disputed issue on infringement – *i.e.*, Sun's product, as labeled for use, is equivalent to the isotonic composition of the '405 claims.[2]

[2] Sun's criticism of Plaintiffs' responses is tenuous at best. Indeed, Sun failed to respond ***at all*** to Plaintiffs' Rule 56.1 Statement in support of their cross-motion for summary judgment. In light of Sun's stark omission, the facts in Plaintiffs' Rule 56.1 Statement should be deemed admitted. *See, e.g.*, *Goodwin v. Martin*, 20078 WL 3026679 at *2-*3 (D.N.J. Oct. 12, 2007) .

B. Sun Ignores the Instruction for How Its Product Must Be Used

Sun relies heavily on the osmolality specification in its ANDA to support its arguments on infringement of the isotonic limitation. (Opp'n at 4). Sun's reliance on the statements in its ANDA is particularly telling because, at the same time, Sun all but ignores the mandatory instructions in its package insert for how the product is to be used. Yet, the instructions for use in Sun's package insert are every bit as important as the product specifications (if not more). The required instructions are an essential part of Sun's product required for FDA approval (*see* Br. at 29-30) that Sun attempts unconvincingly to sweep under the rug.

Sun argues that Plaintiffs "ignore" that the '405 claims require the accused product to be "*both* concentrated *and* isotonic." (Opp'n at 1, emphasis in original). That is not so. Sun's product satisfies both limitations. Sun's composition has the required concentration of nicardipine hydrochloride, and therefore, infringes this limitation of the '405 claims literally. Additionally, Sun's product, which includes sorbitol and the instructions for use, is equivalent to the isotonic composition of the '405 claims. Therefore, Sun's product infringes the isotonic limitation under the doctrine of equivalents.

Sun argues that its concentrated product is "hypotonic, which is basically the opposite of 'isotonic' and, thus, hardly 'equivalent.'" (Opp'n at 1). This argument is unsupported by any expert declaration. Sun's conclusion on what is and is not

equivalent is based solely on lawyer argument that impermissibly collapses literal infringement and infringement under the doctrine of equivalents. Under Sun's theory, a composition could never infringe the isotonic limitation under the doctrine of equivalents because such a solution would either be "hypotonic" or "hypertonic." But this is merely a reworked theory of literal infringement, and there is no reason why the doctrine of equivalents should not apply to the isotonic limitation of the '405 claims.

Moreover, Sun's product is not the "opposite" of isotonic, as Sun contends. (Opp'n at 1). Sun's product includes a mandatory instruction [redacted] With that instruction, Sun's product is not a "hypotonic" composition that is ready for use in patients, as Sun suggests. Instead, it is a product specifically designed to maximize stability of the nicardipine hydrochloride active ingredient during manufacturing and storage, and to be [redacted] exactly as the '405 patent teaches.

C. Sun Identifies No Substantial Difference Between Its Product and the '405 Composition

Sun states that its product is "very different" from Cardene® I.V. (Opp'n at 11). However, Sun's arguments regarding alleged differences are inconsistent with its representations to the FDA regarding the comparability of its product to Cardene® I.V. with respect to both safety and stability.

1. Sun Told the FDA That Its Product Is Safe for Use as Labeled

Sun argues that its product [redacted] (Opp'n at 1, 8-9, 11), which is fundamentally an issue of safety. As discussed in Plaintiffs' opening brief, Sun cannot truly believe that this alleged difference poses a meaningful safety concern. Otherwise, Sun would not be able to support its request for FDA approval. (*See* Br. at 3-5, 26-27). As it is currently labeled, there is no substantial safety difference between Sun's product and the composition of the '405 patent. Sun admits as much in its brief when it concedes that "Sun's product is ***perfectly safe*** to administer to patients . . . in the diluted (isotonic) form, ***as set forth in Sun's product label***." (Opp'n at 12, emphasis added).

Sun also attempts to distinguish its product by referring to alleged "off-label" uses of Cardene® I.V. in which the solution is [redacted] (Opp'n at 11). Sun suggests that these off-label uses highlight the significance of the difference between its product and the '405 composition. It is black letter patent law, however, that Sun's product as it is labeled is what is relevant to infringement, not potential off-label uses. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1354-55 (Fed. Cir. 2003). Whether Sun's product can or cannot be used safely off-label is irrelevant to the infringement issues here.

Moreover, as with the labeled uses discussed above, Sun cannot believe that there is a substantial safety concern with its product [redacted]

[redacted] Sun knows that if its product is substituted as a generic equivalent, it will unavoidably be used for the same applications off-label as Cardene® I.V. Yet, Sun has done nothing to warn healthcare providers that the difference in sorbitol in its composition means that its product cannot be injected directly. If Sun truly believed that there was a substantial safety difference, it would be reckless to sit idly by while seeking approval from the FDA to market a product that Sun believes will pose a risk to patients if used off-label in the same way as Cardene® I.V.

2. Sun Submitted Extensive Testing to Persuade the FDA That Its Product Is Stable

Sun argues that the "stability issue" is another "fundamental difference." (Opp'n at 9-10). This argument makes no sense. Sun has told the FDA that its product has comparable stability as the preferred embodiment of the '405 patent (Cardene® I.V.). Indeed, Sun has gone to great lengths in its ANDA to persuade the FDA that this is so. (Br. at 14-16). Specifically, Sun told the FDA that the nicardipine hydrochloride in its product is [redacted] (*Id.* at 14-15; RW Ex. 7 at SPIL 000002). Sun also submitted data to show that its product has comparable stability [redacted] (Br. at 15). Sun's overriding goal during development was to obtain comparable stability by using exactly the same ingredients in exactly the same way as the preferred embodiment of the '405 patent. (*Id.* at 11-17).

3. Sun's Admissions Regarding Bioequivalence Are Highly Relevant

Sun argues that its admissions regarding the bioequivalence of its product to Cardene® I.V. have "nothing to do" with infringement. (Opp'n at 2). That is not so. Sun's representations to the FDA regarding bioequivalence are directed to the stability and safety of its product. In turn, bioequivalence is relevant to the infringement issues in this case because Sun has identified safety and stability as the differences that allegedly distinguish its product from the '405 composition.

As Sun acknowledges, bioequivalence means that the rate and extent to which its product delivers the nicardipine hydrochloride active ingredient to the body is comparable to Cardene® I.V. (Opp'n at 11). And, as Sun is well aware, the FDA uses bioequivalence as a benchmark to support the conclusion that a generic product will have comparable safety and efficacy to the brand. *See* 21 U.S.C. §355 (j)(2)(A)(iv); 21 C.F.R. §314.94 (a)(7). As a result, the FDA does not ordinarily require clinical trials in humans to demonstrate safety and efficacy before a generic can be approved. Instead, the generic manufacturer, if it can establish bioequivalence, may rely instead on the results of clinical studies performed earlier by the brand manufacturer. This is one of the principal benefits with respect to time and cost savings for the development of a generic product.

In this case, Sun performed a study in healthy volunteers in an attempt to show that its composition is bioequivalent to Cardene® I.V. (*See* Br. at 15-16).

Sun relied on the results of that study to persuade the FDA that its product should be approved because it has comparable safety and efficacy to the brand. (*See* RW Ex. 12 at SPIL 028447, 28453). Sun's representations regarding bioequivalence are directly relevant to the infringement issues in this case because they are admissions that Sun's scientists do not believe that the safety and stability differences identified by Sun's attorneys are substantial. Thus, Sun's arguments in this litigation directly contradict its representations about bioequivalence in support of FDA approval.

Finally, Plaintiffs never argued that bioequivalence is ***per se*** the same as infringement under the doctrine of equivalents, as Sun contends. (*See* Opp'n at 2, 10-11). The cases that Sun cites (*see* Opp'n at 10-11) do not even come close to addressing evidence of bioequivalence in situations like this one where the accused infringer has identified stability and safety as allegedly substantial differences. Sun attempts to draw a general conclusion regarding evidence of bioequivalence, but ignores the pertinent facts of this case.

III. PLAINTIFFS ARE NOT ESTOPPED FROM ASSERTING THE DOCTRINE OF EQUIVALENTS

Contrary to Sun's arguments (*see* Opp'n at 6-10), there is no legal limitation that precludes the application of the doctrine of equivalents. Sun's contentions are essentially reworked literal infringement arguments. Such literalism is exactly what the doctrine of equivalents was designed to foreclose.

A. Plaintiffs Do Not Read Out the Isotonic Limitation

The conclusion that Sun's product infringes under the doctrine of equivalents does not "erase" the isotonic limitation from the '405 claims, as Sun contends. (*See* Opp'n at 8-9). Sun adds [redacted] to help stabilize the nicardipine hydrochloride active ingredient. But [redacted] Sun merely [redacted] Sun is able to do so because [redacted] makes no difference from a stability or safety point of view. Thus, rather than reading out the isotonic limitation, Sun's substitution of one element of the claimed composition for something else that is insubstantially different is a classic situation where the doctrine of equivalents applies. *See, e.g.*, *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 610-612 (1950); *Voda, M.D. v. Cordis Corp.*, 2008 WL 3822801, at *13 (Fed. Cir. August 18, 2008).

The cases that Sun cites do not apply to the facts here. (*See* Opp'n at 8 n.3). Those cases involve more than just the substitution of one element for another, as Sun has done in this case, but also include limiting statements in the patent or prosecution not found here. Also, Sun attempts to draw a parallel between the ranges in the claims of the cited cases that is inapposite. The '405 claims recite no

range for isotonicity. In its proposed construction of "isotonic," Sun imports a range for osmolality from secondary sources that is not found anywhere in the '405 patent. (Br. at 21-22). Sun then attempts to rely on that imported range to argue that its product does not infringe. But there is no dispute that the [redacted] Sun's product results in an isotonic solution when [redacted] (*Id.* at 26, 30-31). Thus, Sun's product, as it is labeled for use, is equivalent to Sun's proposed range of osmolality, even if that range were part of the '405 claims (which it is not). The [redacted] merely [redacted] which is insubstantially different from the isotonic composition of the '405 claims.[3]

B. The Inventors Did Not Surrender Administration by Infusion

Sun argues that the '405 claims exclude compositions that are injected by infusion. (Opp'n at 1, 3, 8-9 n.4). Sun's reading of the '405 patent is unsupported attorney argument that is inconsistent with the plain language of the '405 claims and the description of the invention in the specification and prosecution history.

[3] Sun argues that the evidence in this case actually pertains to indirect, not direct, infringement. (Opp'n at 7). That is not so. Sun performs each and every one of the acts necessary for direct infringement. Sun adds sorbitol to stabilize its product. Sun packages its composition with the instructions for use. There is no need for Plaintiffs to rely on indirect infringement when the evidence of direct infringement is clear and straightforward.

1. The '405 Claims Encompass Direct Injection and Injection by Infusion

Sun attempts to read "direct injection" into the term "suitable for parenteral administration." (Opp'n at 8-9). But parenteral administration is not limited to direct injection from the ampul, as Sun contends. It encompasses direct injection or injection by infusion. This meaning is clear from the '405 specification, which pointedly distinguishes oral administration from parenteral administration without specifying any particular method of injection. (RW Ex. 1 at 1:30-44). The specification further describes how the inventors solved numerous problems associated with injectable nicardipine hydrochloride compositions, including compositions that are administered by infusion. (*Id.* at 9:1-10:33). It would make no sense for the inventors to solve problems in the prior art with compositions for infusion and then exclude them from the scope of the '405 claims. Indeed, Sun's argument would inexplicably carve out the preferred embodiment, Cardene® I.V., which is only approved for administration by infusion.

Finally, the construction of "parenteral administration" as including both direct injection and injection by infusion is how a person of ordinary skill would understand the term in practice and in the '405 patent. (TF Ex. 1 at ¶¶ 132-135). Sun has submitted no expert declaration to the contrary. Notably, Sun describes its own product as a [redacted] even though it is labeled only for [redacted] (RW Ex. 7 at SPIL 000002; RW Ex. 9).

2. There Was No Disclaimer During Prosecution

Sun argues that the inventors gave up coverage of compositions that are administered by infusion when they described the invention during prosecution as "injectable." (Opp'n at 3, 9, 10). But like the term "parenteral administration," the term "injectable" encompasses both direct injection and injection by infusion. Indeed, that is how Sun uses the term when it identifies its product as [redacted] (RW Ex. 7 at SPIL 000001-2, emphasis added).

There was no "clear and unmistakable" surrender of subject matter, as Sun contends, because the inventors never had to distinguish their stable nicardipine compositions on the basis of whether they are injected directly or by infusion. *See Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1325-26 (Fed. Cir. 2003). Instead, the inventors demonstrated that they were able to stabilize nicardipine hydrochloride solutions at concentrations of "at least about 1 mg/ml," something that no one in the prior art had ever been able to achieve before.

IV. CONCLUSION

For the foregoing reasons and the reasons set forth in its opening brief, Plaintiffs respectfully request that the Court deny Sun's motion for summary judgment and grant their cross-motion for summary judgment of infringement.

Respectfully submitted,

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